REMARKS

Claims 1, 15, 21-24, 26-28, 30-38, and 61-71 were pending in the instant application. The Examiner has withdrawn claims 32-38 as drawn to a non-elected species. Applicants have amended claim 15, and have added new claims 72-73, for clarity and to more particularly point out and distinctly claim that which the Applicants regard as the invention. Applicants have amended claim 24 to correct an obvious editorial informality. Applicants have canceled claims 1, 26 and 61 without prejudice and reserve the right to pursue the subject matter of the canceled claims in one or more related applications. Applicants have added new claim 72 to encompass the subject matter of canceled claim 1. Support for the amendments to the claims and for new claims is found throughout the specification as filed. For example, support for the amendments to claim 15 may be found in paragraphs [0019] and [0020] at page 5 and in paragraph [0038] at page 10; support for new claim 72 may be found in paragraph [0041] at page 11; and support for new claim 73 may be found in paragraph in paragraphs [0019] and [0020] at page 5 and in paragraph [0038] at page 10. Accordingly, no new matter has been introduced. After entry of this amendment, claims 15, 21-24, 27-28, 30-38, and 62-73 will be pending.

The rejections under 35 U.S.C. § 112, first paragraph, should be withdrawn

The Examiner has rejected claims 1, 15, 21-24, 26-28, 30-38, and 61-71 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Preliminarily, Applicants note that claims 1, 26 and 61 have been canceled, rendering the instant rejection moot with respect to these claims. The Examiner first contends that the specification has not sufficiently described or provided sufficient examples to support the generically claimed "secretase inhibitor." However, the Examiner has recognized that the specification is sufficient to support the "subgenus of protease inhibitors which inhibit APP processing." Although not agreeing with the Examiner's contention of lack of support for secretase inhibitors, generically, Applicants have amended claim 15, the sole remaining independent claim, such that it is now drawn to a method comprising the use of the class of secretase inhibitors indicated as supported by the Examiner: a method comprising the use of a secretase inhibitor that inhibits γ-secretase or β-secretase processing of amyloid precursor protein (APP).

Secondly, the Examiner alleges that the rejected claims fail to satisfy the written description requirement because the claims are directed to the treatment of a "solid tumor," which term is not adequately supported. Applicants respectfully disagree with the Examiner's contention. An adequate written description of the solid tumor of the claimed method does not

require that the specification provide a detailed characterization of every, or even most, species of solid tumors, for the reasons set forth below.

The Examiner's attention is directed to the Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112 ¶ 1, "Written Description" Requirement" ("the Guidelines") (published in the January 5, 2001 Federal Register at Volume 66, Number 4, pages 1099-1111). The Guidelines specify that there are situations where description of even one species adequately supports a genus. "Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (*Id.* at page 1106, col. 3, lines 42-50). Where the specification discloses any relevant identifying characteristics, *i.e.*, physical, chemical and/or functional characteristics, sufficient to allow a skilled artisan to recognize the applicant was in possession of the claimed invention, a rejection for lack of written description under Section 112, first paragraph, is misplaced.

The case law on which the Examiner based his rejection discussed written description requirements in the context of claiming nucleic acids. In particular, the Examiner relied on The Regents of the University of California v. Eli Lilly, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied,* 523 U.S. 1089 (1998), wherein the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. Applicants respectfully point out that this holding regarding a genus of nucleic acids is not applicable to the instantly claimed invention, as discussed below. *Eli Lilly* concerns claims directed to genera of vertebrate and mammalian insulin cDNAs based merely on the disclosure of a single species, rat insulin cDNA, a prophetic method for obtaining another species (human insulin cDNA), and the functional activity of the other species in the claimed genera. *Id.* The court in *Eli Lilly* held that a "description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs,...or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus" [footnote omitted]. *Id.* at 1569.

The instant application is clearly distinguishable from that in Eli Lilly in that the specification provides exemplary tumors (see specification, paragraph [0024] at page 6 and in paragraph [0051] at page 13) and describes that a method of reducing one such solid tumor volume by inhibiting angiogenesis had been successfully performed (Example 3, page 20).

Moreover, the specification further defines the solid tumors of the claimed method by contrasting solid tumors to other "proliferative disorders" (see, *e.g.*, paragraph [0024] at page 6 and in paragraph [0051] at page 13). The proliferative disorders indicated in the specification include hemoatopoietic disorders such as leukemias and lymphomas. When read by one of ordinary skill in the art, the separation of tumors from the exemplified "proliferative disorders" indicates that tumors are distinct from non-solid malignancies. Because the "solid"/"non-solid" dichotomy is described in the specification, and, more importantly, well established in the art of cancer research (see, *e.g.*, Tsuro et al., 2003, Cancer Sci. 94:15-21, previously submitted as reference **C20** in the Supplemental Information Disclosure Statement submitted October 23, 2007), Applicants respectfully submit the specification provides the physical, structural features common to the members of the genus of tumors encompassed by the claimed method, which features give rise to a written description of the genus, as well as provides the identifying characteristic of association with pathological angiogenesis.

Given the physical descriptions of the tumors (*e.g.*, angiogenic dependence), and the teaching of particular tumors in the specification, Applicants submit that the specification provides an adequate written description of the solid tumors of the claimed methods given the appropriate standard elucidated above.

In view of the foregoing, Applicants submit that the rejections under 35 U.S.C. § 112, first paragraph, have been obviated or overcome and request withdrawal of the rejections.

The rejections under 35 U.S.C. § 102 should be withdrawn

The Examiner has rejected claims 15, 21 and 71 under 35 U.S.C. 102(b) as allegedly anticipated by Blanco-Aparicio et al., 1998, J Biol Chem 12370-12377 ("Blanco"). The Examiner contends that Blanco teaches a method of reducing solid tumor volume in an animal or human comprising the use of at least one secretase inhibitor. Applicants respectfully traverse the rejection.

Blanco teaches the use of potato carboxypeptidase inhibitor (PCI) to inhibit the growth of xenografts in an *in vivo* model of pancreatic cancer. However, Blanco does not disclose or teach A) the use of a secretase inhibitor generally, B) that PCI is a γ-or β- secretase inhibitor or C) that PCI inhibits γ- or β-secretase processing of APP as instantly claimed in claim 15. Secretases cleave transmembrane proteins to produce peptide fragments thereof that are no longer tethered to the cell membrane; carboxypeptidases are involved in protein maturation and merely

hydrolyze the C-terminal peptides of polypeptide chains. Potato caboxypeptidase is not a secretase, much less a γ- or β-secretase, and the Examiner has not come forward with any evidence that would link PCI to the inhibition of γ- or β-secretase activity disclosed in the specification. Accordingly, Applicants respectfully submit that Blanco is not at all relevant to the instant claims and, thus, does not teach each and every element of claim 15 as amended herein. Because Blanco does not teach each and every element of claim 15, the reference cannot anticipate claim 15 or claims 21-24, 27-28, 30-38, and 62-73 as dependent thereon.

In view of the foregoing, Applicants submit that the rejections under 35 U.S.C. § 102 have been obviated or overcome and request withdrawal of the rejection.

The rejections under 35 U.S.C. § 103(a) should be withdrawn

The Examiner has rejected claims 15, 21-24 and 62-71 under 35 U.S.C. § 103(a) as allegedly obvious, separately, over Blanco, Weng et al., 2003, Mol. Cell Biol. 23:655-664 ("Weng") or Jundt et al., 2002, Blood 100:158 ("Jundt"). The rejection is predicated on the assertion that Blanco, Jundt or Weng provides motivation to use a secretase inhibitor to reduce the volume of a solid tumor in an animal or human. Applicants respectfully disagree with the Examiner's contentions.

In contrast to any of Blanco, Weng or Jundt, the instant inventors have surprisingly discovered that administration of compounds of the invention is able to effect a reduction in tumor volume in an *in vivo* model system. In particular, the specification discloses that intraperitoneal administrations of compounds of the invention were able to achieve an over 90% reduction in tumor size over treatment duration (see, specification, Example 3 at page 20 and Fig. 8). As discussed in detail below, none of Blanco, Weng or Jundt teach or disclose similar tumor-reducing effects of secretase inhibitors and, thus, none can suggest a means of reducing tumor volume as instantly claimed in claim 15 or claims 21-24, 27-28, 30-38, and 62-73 as dependent thereon.

As discussed above, Blanco is directed to the use of PCI to effect growth control in an *in vivo* model of pancreatic cancer. However, PCI is not a secretase inhibitor generally, much less a specific inhibitor of γ- or β-secretase, nor is there evidence that PCI inhibits γ- or β-secretase processing of APP as instantly claimed in claim 15. Because Blanco is entirely irrelevant to the instant claims, it cannot teach or suggest the method of claim 15 or any claim dependent thereon.

Weng discloses the use of recombinant T cell lines transformed to express Notch-

constructs in a study of Notch signaling in regulation of cell growth and differentiation. In particular, Weng reports that presenilin inhibitors alter processing of the Notch constructs and that one specific such inhibitor, DPF-AA, was able to inhibit the growth of one of the recombinantly created cell lines. However, as figure 3 demonstrates (see, Weng at page 658), treatment with the presenilin inhibitor merely suppressed the growth rate of target cells. Treated cells initially proliferated at the same rate as controls, which rate eventually slowed such that the cultures exhibited a plateau phase, characterized by a constant concentration of viable cells. The constant concentration of viable cells suggests either that the cultures have stopped proliferating, *but remain viable*, or that the presenilin inhibitor is in fact cytotoxic, but achieving a death rate that is only sufficient to balance the proliferative capacity of the cells, which remains unaffected. Thus, Applicants submit that one of ordinary skill in the art would interpret the teachings of Weng as merely suggestive of a means of slowing cancer cell proliferation or, at most, a means of preventing further growth of the existing tumor burden at treatment start. Thus, Weng cannot suggest a means of reducing solid tumor volume as instantly claimed in claim 15

As with Blanco and Weng, Jundt also fails to render obvious the method of reducing solid tumor volume as instantly claimed. Jundt is directed to a characterization of Jagged1-Notch signaling in Notch-positive Hodgkin and large cell anaplastic lymphoma cell lines. In the sole inhibition study presented, Jundt reports that, *in vitro*, exposure of these cell lines to Jagged1 results in an exponential increase in the cells' respective growth rates, which effect is blocked by the γ-secretase inhibitor, DAPT. Notably, however, Jundt reports that only that the increase in growth rate caused by Jagged1 exposure is blocked by DAPT, suggesting that DAPT does not affect the original proliferative capacity of the cells. Accordingly, like Blanco and Weng, Jundt is, at most, suggestive of a method to slow cancer cell growth, or perhaps maintain tumor volume, but not to effect a reduction in tumor volume as instantly claimed.

Thus, Applicants submit that none of Blanco, Weng or Jundt is suggestive of a method to reduce solid tumor volume as instantly claimed in claim 15 and in claims 21-24, 27-28, 30-38, and 62-73 as dependent thereon.

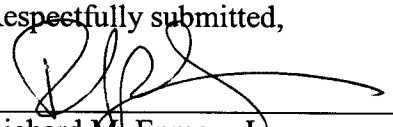
In view of the foregoing, Applicants submit that the rejections under 35 U.S.C. § 103(a) have been obviated or overcome and respectfully request withdrawal of the instant rejections.

CONCLUSION

Applicants respectfully request that the amendment and remarks made herein be entered and made of record in the instant application. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

Date: July 23, 2008



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